Network analysis of symptoms in a Parkinson patient using experience sampling data

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RESEARCH ARTICLE

Network Analysis of Symptoms in a Parkinson Patient Using Experience Sampling Data: An n = 1 Study

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ABSTRACT: Background: Around 50% of Parkinson's disease patients experience motor fluctuations after long-term treatment with levodopa. These fluctuations may be accompanied by mood fluctuations. Routine cross-sectional assessments cannot capture the extent of these motor and mood fluctuations and their possible associations. Experience sampling techniques that use frequently repeated measurements of symptoms over time are able to capture such fluctuations. Based on such data, longitudinal associations between symptoms can be studied using network analysis.

Aim: The purpose of this study is to identify longitudinal associations between motor symptoms and mood states in a patient with Parkinson's disease.

Methods: A 53-year-old man with Parkinson's disease and motor fluctuations collected experience sampling data during 34 consecutive days. A set of dependent variables included tremor, rigidity, balance problems, and "on/off" state, and the mood variables anxiety, cheerful, and "down." Independent variables were the same variables assessed at the preceding measurement.

Regression coefficients were calculated and presented in a network graph.

Results: In this patient, anxiety and cheerfulness had a central position within the symptom network. Higher anxiety was prospectively associated with increased rigidity and tremor and with feeling "down." Cheerfulness was associated with less tremor. Balance problems were not influenced by cheerfulness nor anxiety, but increased balance problems were associated with reduced cheerfulness at the next assessment. Feeling "down" did not influence self-reported motor symptom severity at the next assessment.

Conclusion: This n = 1 study shows that network analysis of experience sampling data may reveal longitudinal associations of self-reported motor symptoms and mood states that may have relevance for treatment strategies. © 2018 International Parkinson and Movement Disorder Society

Key Words: Parkinson's disease; motor fluctuations; mood; network analysis; experience sampling

Up to 50% of patients with Parkinson's disease (PD) experience motor fluctuations after long-term treatment with levodopa.¹ Such fluctuations in motor symptoms are often accompanied by mood fluctuations.^{2–4}

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Research involving mood fluctuations, their underlying mechanisms, and their relationship with motor fluctuations has so far led to inconsistent results.⁵ Insight into the timing and associations of fluctuations in motor and mood symptoms may provide information that can be valuable for clinical management. The frequency and severity of fluctuating symptoms are, however, difficult to capture in routine cross-sectional assessments, as such assessments use rating scales where a single assessment is considered representative for symptom severity over a longer time frame. Diary assessments can give more clarity, but they are usually completed retrospectively at the end of the day or may hinder people from continuing their everyday activities. The experience sampling method (ESM) is an attractive alternative to diary studies

and cross-sectional assessments.⁶ ESM includes multiple short, repeated, within-subject assessments at random moments during the day. These can include motor symptoms, and mood states as well as contextual information and, therewith, provide a good sample of subjective experiences. The ESM method originated in psychiatry, but has recently been applied in a number of other diseases, such as migraine, stroke, and chronic obstructive pulmonary disease (COPD).^{7–9} Broen and colleagues¹⁰ demonstrated that ESM is also a feasible method for the assessment of mood and motor symptoms in PD patients. When ESM data of a single subject are collected for a longer period of time, network analysis can be performed to study longitudinal relationships between symptoms. In network models, symptoms are conceptualized as mutually interacting, often reciprocally reinforcing elements in a complex dynamic system, also referred to as symptom networks.^{11,12}

The aim of this $n = 1$ study was to explore whether it is possible to identify longitudinal associations between motor symptoms and mood states in a single patient with PD suffering from motor fluctuations using experience sampling data and to generate a symptom network of these associations. We hypothesize that there is a temporal relationship between mood fluctuations and motor fluctuations, with negative emotions (“down,” anxiety) being associated with increased motor symptoms at the next assessment and positive emotions (cheerful) being associated with less motor symptom severity at the next assessment.

Methods

Patient

A 53-year-old man with PD and motor fluctuations was referred to our hospital for a follow-up visit. The patient was diagnosed with tremor-dominant PD in 2011. Since then he has been treated with levodopa/carbidopa. Currently, he takes a dose of 250 mg 4 times daily. In addition, he takes entacapone 200 mg 4 times and pramipexol 1.05 mg once daily. He has been suffering from motor fluctuations since 2015. Initially, these motor fluctuations, predominantly affecting tremor and rigidity, were predictable and involved levodopa-related “wearing-off.” Later, the “on/off” fluctuations became unpredictable. The patient did not suffer from dyskinesias. Upon the start of ESM data collection, the patient was cognitively intact and working part-time as a teacher. Baseline measurements are displayed in Table 1. The patient participated in ESM as part of his clinical assessment and agreed to have the period of data collection extended to 1 month. Informed consent was signed for the extended data collection and for publication of this $n = 1$ study. ESM data were collected from March 16, 2017, to April 18, 2017.

TABLE 1. Patient characteristics at baseline

Measurement	Score/range
Hoehn & Yahr staging ²⁴	2.5/0-5
UPDRS ²⁵	21/0-108
Mini Mental State Examination ²⁶	28/0-30
Parkinson Anxiety Scale ²⁷	17 ^a /0-48
Beck Depression Inventory-II ²⁸	14/0-63
Parkinson's Disease Questionnaire-8 ²⁹	21 ^b /0-31

^aSlightly above the cut-off of 14 for clinically relevant anxiety.

^bIndicating a somewhat reduced quality of life.

ESM Data Collection

The ESM protocol in the present study is based on the routine outcome monitoring of the psychiatric outpatient department of our hospital, but with the following 5 Parkinson-specific items added: tremor, rigidity, walking problems, balance problems (all scored on a 7-point Likert scale, ranging from 1 = not at all to 7 = very), and “on/off” state (dichotomous variable). This protocol was the same that was used earlier by Broen and colleagues.¹⁰ The patient downloaded an ESM app, the Psymate app (www.psymate.nl), on his own smartphone. Before data collection, the patient received an oral briefing and a demonstration to ensure that the app and questionnaire were fully understood. The Psymate app was programmed to emit a signal, a so-called “beep,” 10 times daily at random moments in 90-minute time blocks, between 7.30 AM and 10.30 PM. After each beep, the patient was asked to fill out a 2-minute questionnaire that opened automatically after touching the phone and that consisted of 42 questions regarding his current mood state, the severity of his PD-related complaints, and his surroundings. The questions always appeared in the same order, and although it was not possible to skip single items before continuing to the next question, it was possible to turn back to previous questions and change the answer if necessary. To avoid recall bias, the questionnaires were only available for 15 minutes following the beep. After this timeframe, the patient received a notification regarding the missed questionnaire without the possibility to open and answer the questionnaire. The patient collected data for 34 consecutive days. Two days following the start and in the second week of ESM data collection, the patient was contacted by telephone to inquire about any difficulties or concerns regarding the ESM application and the questionnaire and to answer any additional questions the patient might have.

Statistical Analyses

Statistical analysis and graphical representations were performed using Stata 13¹³ and R.¹⁴ The network analysis performed does not identify causal relationships,

but merely temporal relationships that may or may not be causal. All data in this analysis are from a single participant. Therefore, the data do not have a multilevel structure and can be analyzed with standard linear regression techniques, as opposed to group-level analyses in ESM studies.¹⁵

To assess variation over time, mean daily severity levels of mood and motor symptoms were plotted (Supplementary Figures 1A and 1B, respectively). Floor and ceiling effects were checked using histograms (available on request). For the present analysis, the affective items cheerful and “down,” which reflect opposite poles, were a priori selected as representatives for positive and negative moods, respectively. The affective item anxiety was added based on the presence of clinically relevant anxiety at baseline. Tremor, rigidity, and balance problems were selected for the analysis as the most disabling PD-related symptoms. The patient did not experience any gait problems or dyskinesias. Hence, these symptoms were not included in the analysis.

Six linear regression models were analyzed with cheerful, “down,” anxiety, tremor, rigidity, and balance problems as dependent variables. In addition, 1 logistic regression analysis was performed with “on/off” state as the dependent variable. The “off” state was patient rated and defined as the state in which he experienced no effect of anti-Parkinson medication. Because regression coefficients of linear and logistic regression cannot be combined in 1 network graph, the analysis with “on/off” as the dependent variable was repeated with linear regression as has been done in a previous study.¹⁶ As the results, in terms of statistical significance, were very similar between the 2 analyses, the linear regression results were used to generate the network. Independent variables were the lag ($t-1$) of the same 7 variables added to the regression model simultaneously. In addition, a time variable was added to all regression models (consecutive number for beep-code to take into account time trends). This resulted in 49 regression coefficients. The first assessment of a new day, as well as assessments with a lag longer than 180 minutes from the previous assessment (ie, when the participant missed 1 or more beeps) were excluded from the analysis. Given the exploratory nature of this study, no correction for multiple comparisons was performed.

Using the qgraph command in R, the 49 regression coefficients were presented in a network graph. In this network, the nodes represent the variables and the connections between the nodes represent the regression coefficients. The thickness of the connections reflects the strength of the regression coefficient. In addition, indices of centrality were calculated using Excel (Microsoft, Redmond, Washington) and the qgraph package. In this context, “centrality” is an indicator of

TABLE 2. Descriptive statistics of experience sampling method assessment of variables included in the analysis

Variable	N	Mean	Standard deviation	Minimum	Maximum
Total					
Cheerful	121	5.0	0.49	3	6
“Down”	121	3.0	1.03	1	5
Anxiety	121	1.2	0.66	1	5
Tremor	121	1.9	0.87	1	6
Rigidity	121	1.7	0.90	1	6
Balance problems	121	1.4	0.71	1	5
“On/off” state, %	121	81% on time	n.a.	n.a.	n.a.
Network analysis					
Cheerful	57	4.9	0.52	3	6
“Down”	57	3.0	1.08	1	5
Anxiety	57	1.1	0.54	1	5
Tremor	57	1.8	0.93	1	6
Rigidity	57	1.7	1.03	1	6
Balance problems	57	1.5	0.87	1	5
“On/off” state, %	57	88% on time	n.a.	n.a.	n.a.

Items were scored on a 7-point Likert scale (ranging from 1 = not at all to 7 = very). For “on/off” state, the values 1 and 0 represent “on” state and “off” state, respectively. n.a., not applicable.

how central a specific variable is in the network. As in previous work, centrality indices are defined as follows: the outward strength is the sum of the connections from a specific node to all other nodes.^{17,18}

The inward strength is the sum of the connections from all nodes to 1 specific node. The self-loop is the connection between a node at time point $t-1$ and that same node at time point t . In both the inward and outward strengths, the self-loop is included. The sum of the outward and the inward strengths represents the node strength. Closeness, another measure of centrality, involves the sum of the length of the shortest paths between the node and all other nodes in the graph. Hence, the more central a node, the closer it is to all other nodes.

Results

ESM Data

During the course of 34 days, the patient received a total of 340 beeps. He answered 136 beeps, corresponding to a response rate of 40%. There were some partial missing data as a result of uncompleted questionnaires, resulting in 121 completed assessments and a response rate of 36%. The response rate declined during the course of ESM data collection and varied from 47% in week 1 to 29%, 46%, 36%, and 19% in weeks 2, 3, 4, and 5, respectively. In 23 of the 121 assessments (19%), the patient was in the “off”-state. A total of 57 beep assessments were answered within 180 minutes of a previous beep assessment and were selected for the

FIG. 1. Symptom network. Network graph displaying prospective associations between the mood states 'cheerful', 'down' and 'anxiety', and Parkinsonian symptoms (tremor, rigidity, balance problems and on/off state). Negative regression coefficients are red, positive coefficients green. Significant coefficients are marked with an asterisk. The position of the variables within the graph is a measure of centrality. [Color figure can be viewed at wileyonlinelibrary.com]

network analysis. The average time between beeps was 98.9 minutes (standard deviation = 44.8; range 15.6–176.7 minutes). Descriptive statistics are provided in Table 2. An example of fluctuations of included items during the course of a single day is plotted in Supplementary Figure 2. Except for a floor effect for anxiety, there were no strong floor effects and no ceiling effects.

Network Graph

Cheerfulness and anxiety had central positions within the symptom network (Fig. 1). A network graph displaying the significant associations only is plotted in Supplementary Figure 3. Anxiety was associated with higher scores for tremor ($B = 0.61$, $P = .001$) and "rigidity" ($B = 0.47$, $P = .013$) at the next assessment as well as with feeling less cheerful ($B = -0.40$, $P = .037$) and more "down" ($B = 0.52$, $P = .003$). Cheerful was associated with lower scores for tremor ($B = -0.55$, $P = .002$) and rigidity ($B = -0.38$, $P = .037$) at the next assessment. Balance problems were not predicted by cheerfulness ($B = 0.05$, $P = .78$) or anxiety, but instead more balance problems led to lower scores on cheerful at the next assessment ($B = -0.50$, $P = .011$). In contrast, feeling "down" did not influence motor symptom severity at the next assessment, or vice versa. "On" and "off" states could not be predicted by motor symptoms, but anxiety was associated with "off" at the next assessment ($B = -0.37$, $P = .024$). In addition to associations between different variables, self-loops were created that

reflected the relationship between the severity of the same symptom at the next assessment. The self-loops of cheerful ($B = -0.66$, $P = .001$), anxiety ($B = 0.59$, $P = .000$) "down" ($B = 0.38$, $P = .006$) and balance problems ($B = 0.58$, $P = .003$) were statistically significant.

Centrality indices are provided in Table 3. Anxiety had the highest node strength with a value of 4.79, followed by cheerful with a value of 4.42. "On/off" state had the lowest node strength with a value of 1.77. Closeness was highest for anxiety, cheerful, and balance problems, indicating that those 3 nodes were closest to all other nodes in terms of strength.

Discussion

Interpretation of Results

With this $n = 1$ study we showed that network analysis of ESM data can be used to prospectively reveal associations between motor and mood states in PD. In the symptom network of this patient, the variables of anxiety and cheerful appeared to play a more important role than the variable "down" because they had stronger associations with several motor symptoms and had the highest node strength and closeness index. The centrality of mood variables in the symptom network indicates that affect plays an important role in the way motor symptoms are experienced and reported and even predict symptom severity prospectively. Whereas most studies in PD have focused on the effect of (fluctuations in) motor symptoms on mood, this finding shows that it is as important to understand the role of psychological factors and mood states in predicting self-reported symptoms in PD.

"On/off" state had the lowest node strength, corresponding to the finding that "on/off" state could not be predicted from motor symptoms or affective states and appears to be relatively independent from other variables, except for anxiety. This finding is consistent with the notion that motor fluctuations usually start as end-of-dose deterioration, but tend to become random and unpredictable in the later course of the disease, as was the case with our patient. This unpredictability is also reflected by the fact that the variable "on/off" does not have a self-loop in the network graph. As a general comment, based on the outcome in this patient, it may

TABLE 3. Centrality indices

Variable	Closeness	Inward strength	Outward strength	Node strength
Cheerful	0.038	1.90	2.51	4.42
"Down"	0.028	1.94	1.27	3.21
Anxiety	0.048	1.73	3.05	4.79
Tremor	0.017	1.72	0.48	2.20
Rigidity	0.024	1.40	0.96	2.37
Balance problems	0.036	0.97	1.65	2.62
"On/off" state	0.022	1.00	0.77	1.77

be worthwhile to study the role of anxiety in predicting “off” states.

Despite the data not being multilevel, there can be autocorrelation between consecutive assessments or between assessments on the same day; the shorter the time between 2 assessments, the higher the correlation. The regression coefficients of the balance problems and cheerful self-loops indicate high autocorrelation. The negative regression coefficient in cheerful (-0.66) is surprising and one can only speculate about potential explanations. It may be that the already high score on cheerfulness reduces the chance of scoring even higher at a next assessment. Although the variable time was included in the analysis, it was not possible to further control for autocorrelation as only 1 patient was included.

Data Quality

The Psymate app is available as an app for smartphones or other electronic devices, such as iPods. The patient opted for downloading the app on his own smartphone rather than using one of the available iPods. Previous studies have not shown any difference in compliance between the 2 devices.¹⁰ For this patient, the response rate was 36%, which is above the 33% generally considered valid for analysis.^{15,19} Because it was not possible to skip single items in the questionnaire, thereby preventing selective missingness, all missing values were solely the result of missed beeps and incidentally by not finishing a questionnaire. Missed beeps can be mostly explained from an inability to answer questionnaires as a result of other activities, such as being in traffic or working. However, it also reflects that collecting ESM data during a longer period of time can be burdensome, resulting in lower response rates over time as observed in this patient. The patient was contacted once weekly during the first 2 weeks and at the end of data collection. As the response rate was still sufficient during the first 2 weeks, motivational issues were not addressed. A lack of motivation might have contributed to the low response rate in the final weeks of data collection. Regular weekly contact during ESM data collection might increase response rates, especially when data are being collected for a longer time frame. In future studies, it might also be worthwhile to evaluate a patient's experience with ESM to get more insight into compliance.¹⁰

During the last 2 weeks of data collection, the patient reported stable levels of cheerfulness (Likert score 5) and less fluctuations in motor symptoms. One could argue this created bias and that the patient only responded to beep assessments when feeling cheerful or refrained from answering questions during periods with severe motor symptoms. However, during the same period of data collection, there was a high degree of variation in “down,” which makes cheerfulness bias

unlikely. Also, the higher response rate in the first period, during which the patient reported varying levels in motor symptom severity, ranging from 1 to 6, shows that experiencing more severe symptoms did not lead to reduced response. The present data do include various beeps where the patient is in the “off” state. Therefore, we expect that the network is representative for a large proportion of the time.

Methodological Issues

To our knowledge, this is the first study to use long-term ESM data collected in a single patient with PD to study longitudinal associations between motor and mood symptoms. This exploratory study has, however, several limitations. First, the response rate of 36% was low. Earlier ESM studies suggest that at least 33% of the assessments need to be completed for their data to be considered valid.^{15,19,20} Preferably, prospective associations are studied between 2 successive beep assessments. As this would result in too few usable assessments, assessments were considered valid if they were within 180 minutes of a previous beep, regardless of whether there was a missed beep in between. Although the resulting selection of 57 couples of beep assessments for the network analysis, of which 7 were in the “off” phase, does not influence the representativeness of the data, it does result in lower power. Because of the reduced response rate in the last weeks of data collection as well as the more stable scores on cheerfulness in that period, we performed a sensitivity analysis based on the data of the first 20 days of sampling, which resulted in a very similar network (see Supplementary Figure 4). Second, although we looked at node strength and closeness as measures of centrality, betweenness as measure for centrality was not determined for this study. Bak and colleagues,¹⁷ who used network analysis in a patient with recurrent psychosis, showed that the importance and clinical relevance of betweenness as an indicator of network performance is low in this type of analysis. In their analysis, as well as in ours, all paths between variables are considered important and the length of various paths can be very similar, whereas betweenness only reflects the shortest path between variables. Third, when performing network analysis including lags, there is a time axis in the analysis. However, even with the time axis only temporal associations can be shown and it does not indicate causality. Finally, the patient did not collect more objective measures of motor functioning.

Clinical Implications

The ultimate aim is to provide patients with optimal and personalized care to reduce their suffering and increase their well-being. ESM can be used for this purpose by generating treatment-relevant information

specific for that patient that cannot be obtained by commonly used cross-sectional assessment methods and rating scales. Previous studies using network analysis for different diseases have demonstrated that ESM data can be incorporated into a personalized treatment plan and facilitate decision-making in a collaborative process.^{15,17,21} For PD patients, ESM data can provide insight into the relationship between different variables and symptom severity. This particular network analysis focused on mood variables, but based on the specific situation of the patient, other relevant variables can be included in the network. Contextual variables, such as present company, whereabouts, and activities, can provide information on whether symptoms worsen or improve in specific situations. This information can be valuable for both patients and physicians or other members of the patient's healthcare team, as it may give more insight into determinants of the patient's symptoms and may lead to (nonpharmacological) treatment recommendations. For example, when affective states or contextual factors appear to play a central role in self-perceived motor symptom severity, it may be preferable to treat the mood state or to improve coping with the specific situation. Based on the network analysis of ESM data in the present study, our patient was offered individualized face-to-face feedback regarding the specific connections in his symptom network and in particular regarding the possible role of positive emotions in improving self-perceived motor symptoms. However, the patient preferred to receive a written report of the results as he was limited in his time. We do not know whether a lack of motivation contributed to his decision of not desiring a face-to-face meeting or whether the patient benefited from the provided information. For future studies it would be interesting to use ESM data sampling to develop a treatment plan with personalized interventions and to use postintervention ESM data sampling to study the effectiveness of the intervention. It may also be valuable to combine ESM with downloadable apps or wearable devices that are able to objectively quantify motor symptom severity, such as severity of tremor or poverty of movement. This is technically feasible and will provide information that, when combined with ESM, will allow comparison between the objectively measured severity of the tremor, and the subjectively experienced severity of tremor.²² Integrating these measurements could then be useful for fine-tuning future therapies such as closed-loop deep brain stimulation systems.²³

Conclusion and Recommendations

In this $n = 1$ study, we showed that network analysis of ESM data can be used to sample moment-to-moment variability and to prospectively reveal relevant

associations between motor and mood variables in an individual patient. These prospective associations may be different for different patients. When network patterns in a single patient can be replicated in other PD patients, this may lead to more general treatment recommendations. To reveal such network patterns, multiple $n = 1$ studies with extensive data collection may be superior to ESM studies that include more patients but collect data for a briefer period of time. More research into the usefulness of ESM as a therapeutic tool is warranted. ■

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.